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Response to Crizotinib Rechallenge after Initial Progression and Intervening Chemotherapy in ALK Lung Cancer

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Anaplastic lymphoma kinase rearranged (ALK+) non–small-cell lung cancer has shown remarkable sensitivity to crizotinib.[1] The utility of rechallenge with crizotinib after progression and time on other therapies has not previously been described.

A 63-year-old, white, female never-smoker had a stage IIIA adenocarcinoma resected by pneumonectomy after neoadjuvant carboplatin and paclitaxel. Eight months later, she experienced widespread recurrence at various sites including right adrenal, right kidney, and abdominal lymph nodes.

Molecular analysis revealed ALK positivity by fluorescence in situ hybridization.[1] In August 2009, she commenced crizotinib (250 mg twice daily).[1] After 2 months, her right renal lesion decreased in size by 50% per Response Evaluation Criteria in Solid Tumors, and all sites of disease showed decreased metabolic activity. In April 2010, she had isolated progression in the right adrenal and received 30 Gy to this site using stereotactic body radiotherapy with continuation of the crizotinib. In August 2010, she progressed in a left retroperitoneal lymph node and received additional stereotactic body radiotherapy. Positron emission tomography and computed tomography (PET/CT) in January 2011 showed improvement in the areas treated with radiotherapy but additional progression in retroperitoneal and mediastinal lymph nodes. Crizotinib was discontinued in February 2011.

From February 2011 through June 2012 she received pemetrexed (500 mg/m^2 every 21 days) and achieved complete radiographic response on PET/CT by August 2011. In May 2011, she received stereotactic radiosurgery on two new brain metastases. In June 2012, she developed progression in a right renal lesion, not amenable to radiotherapy, and pemetrexed was discontinued. In July 2012, crizotinib was reinitiated, 250 mg twice daily. After 6 weeks of therapy, a PET/CT showed a decrease in the size of her renal lesion by 44%, and resolution of all hypermetabolic activity (Fig. 1).

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DISCUSSION

Our patient experienced an initial progression-free survival for 8 months, but a total of nearly 18 months of disease control because of crizotinib, using radiotherapy to treat oligoprogressive resistant clones.[2] Our patient then had a prolonged radiographic response to second-line pemetrexed.[3,4] Her dramatic response on rechallenge with crizotinib after 16 months of intervening pemetrexed is reminiscent of the benefit when EGFR mutant patients are rechallenged with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), after a period of time either on non-EGFR–directed therapies or off all therapy.[5] These data suggest that, although TKI-sensitive clones of oncogene-addicted cancers may be dramatically suppressed, they still survive treatment with the relevant TKI. These TKI-sensitive survivors may then re-emerge along Darwinian evolutionary lines under selection pressures that are not directly related to the pathway affected by the TKI. In the acquired resistance setting, continuing the TKI during next-line chemotherapy could be one way of addressing this phenomenon. However, whether a combination approach would be better or worse than sequentially alternating selection pressures is currently unclear. In the crizotinib-acquired resistance setting, rechallenge of ALK+ patients with crizotinib after chemotherapy versus continuation of both chemotherapy and crizotinib together (if tolerable), should be considered for further investigation.

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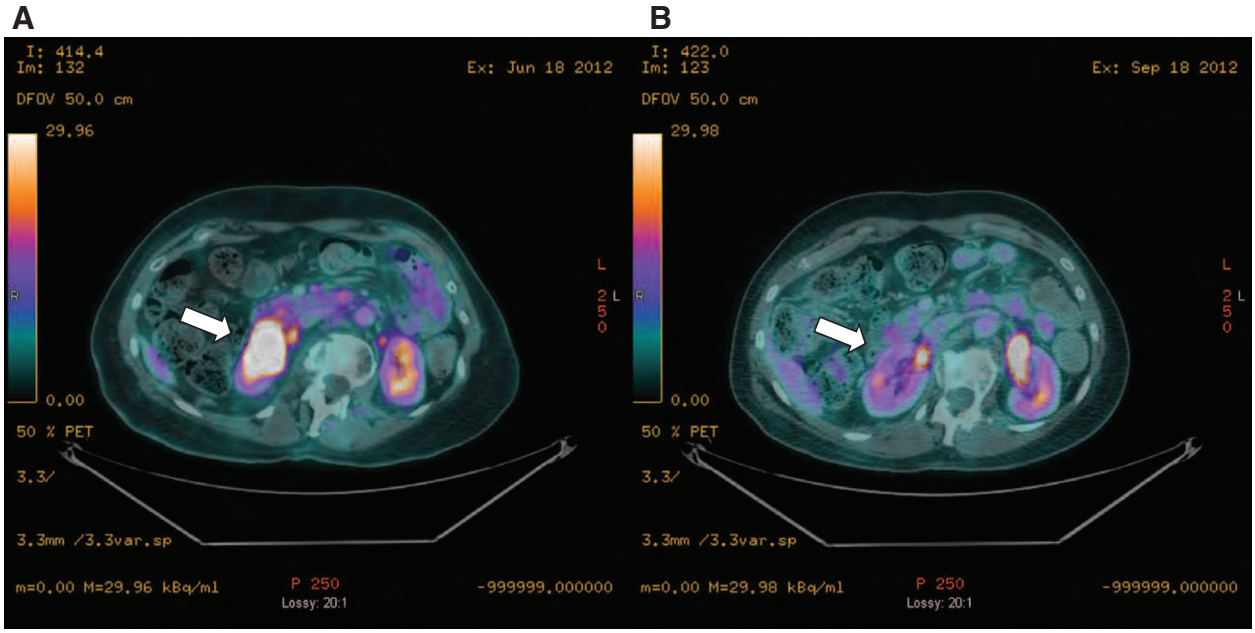

FIGURE 1. *A,* Right renal lesion, which developed on pemetrexed after prior crizotinib, and *(B)*, subsequent response after 6 weeks of crizotinib rechallenge.

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